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A Follow-Up Study of the Effects of Early Malnutrition on Subsequent Development. I. Physical Growth and Sexual Maturation during Adolescence

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ABSTRACT. A follow-up study of growth and development was conducted on 216 Barbadian children aged 9 to 15 yr, half of whom had histories of moderate to severe protein-energy malnutrition in their 1st yr of life. Although index girls had significant delays in sexual maturation and were reduced relative to comparison girls on measures of weight for height, arm circumference, and skinfold thick-

ness, their rate of growth when compared with values obtained 4 yr earlier was equal to or better than that of the comparison group. In contrast, boys in the index group were slightly reduced in height compared with their matched comparisons and had similar patterns of growth and sexual maturation. This study suggests a relationship between an episode of infantile malnutrition and impaired endocrine functioning among girls in the adolescent years. (*Pediatr Res* 19: 518-523, 1985)

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Abbreviations

MANOVA, 2-way multivariate analysis of variance
ANOVA, 2-way univariate analysis of variance

This paper is one of a series of reports describing the long-term consequences of protein-energy malnutrition in the 1st yr of life (1-7). We have previously reported significant deficits in the physical growth of children aged 5 to 11 yr who had histories of malnutrition, especially in the girls of this population (3). Although the index children came from homes which were slightly more disadvantaged than those of comparison children without histories of malnutrition, these socioeconomic conditions measured concurrently did not contribute significantly to the differences in growth between index and comparison children (7). We believe this to be a reflection of the relatively homogeneous Barbadian population and also the possible compensatory role of enrollment in the National Nutrition Centre which followed our index population until 11 yr of age.

Herein we describe the growth of these same children at follow-up 4 yr later, when they were 9 to 15 yr of age, including measures of sexual maturation assessed by the Tanner scale (8, 9). We show that the onset of pubescence is delayed in index girls and this finding is associated with a reduction in mean heights and weights, whereas index boys are no longer small as compared to comparison boys. However, the velocity of growth over this period is highest among index girls.

METHODS

This study was conducted at the National Nutrition Centre in Barbados (10). Since 1967, this center has provided medical care to children with malnutrition from the time of diagnosis to 11 yr of age. All cases of malnutrition in Barbados must be reported to the National Nutrition Centre, and, thus, good documentation is available on a population of approximately 2100 children. Several features of the Barbadian population were favorable to our investigation. First, the delivery and documentation of health care are good. Almost all children are born in the Queen Elizabeth Hospital or allied facilities, and records of obstetric and perinatal care are available in almost all cases. Furthermore, children are followed routinely by local clinics and these records were made available to us. Second, education is almost universal. Nearly all children attend school to 16 yr of age, and 95% of the Barbadian population is literate. Comprehensive school records are available for each child. Third, the population is stable—with little in or out migration—and is largely homogeneous with respect to ethnicity and socioeconomic level, which is mostly lower middle class. Because of all these advantages we were able to obtain extensive documentation of index and comparison children during infancy (including specific details surrounding the episode of malnutrition for index children), early childhood, and at the time of the study.

Study population. In the earlier series of studies, 129 index children of ages 5 to 11 were selected using the following criteria:

- 1) They had been diagnosed on clinical examination by one of our group (F.R.) as showing the symptoms of protein-energy malnutrition, including moderate to severe weight loss (below 75% of expected weight for age) in the absence of edema, during the 1st yr of life. Further episodes of malnutrition are rare in this population, and only children with a single episode were included.
- 2) Their birth weight was at least 5 lb to exclude those children exposed to significant fetal growth retardation.
- 3) They had no evidence of prenatal or perinatal complications, as measured by standard criteria including the Apgar score.
- 4) They had no history of convulsion, head injury, or loss of consciousness.

The index children were hospitalized at the Queen Elizabeth Hospital for a period of 37 ± 15 days and were then followed by the National Nutrition Centre through 11 yr of age, where they received medical care, including home visits, nutritional counseling, and subsidized milk.

The comparison children were for the most part classmates of the index children and were matched to them by sex and age.

Except for the fact that they did not have histories of malnutrition and had documented normal growth during childhood, the comparison children met the same criteria as the index children.

In the present investigation, we have followed the same child population 4 yr later in order to determine changes associated with growth and development into adolescence. We were successful in identifying 109 (or 85% of the original sample) of index children and 107 of the comparison group.

Data collected. Anthropometric measures (11) were obtained at the National Nutrition Centre by two pediatricians who were blind to the nutritional history of the children. Height was measured to the nearest $\frac{1}{2}$ cm with the subject standing (without shoes) and sitting. Children were weighed in the underclothes using an adult Detecto (Long Island City, NY) office scale, which was calibrated prior to each reading. Arm circumference was measured on the left arm at a level halfway between shoulder and elbow. An "insertion tape" was used which has a window through which the end of the tape was pulled. Skinfold thickness was measured using Lange calipers.

Measures of sexual maturation using the Tanner scale (8, 9) were also made by the pediatrician as part of a general medical evaluation. Breast and pubic hair development were assessed in girls and genitalia (penile size and testicular growth) and pubic hair in boys. In each case, maturation was recorded using a 5-point scale, ranging from 1—minimal or no pubescent changes to 5—complete sexual maturation. The number of index and comparison girls in this population who had achieved menarche and the age of menarche were recorded. Physical examination was normal for all children in the study for indices other than growth and sexual maturation, and consequently there were no significant differences between index or comparison groups.

Statistical analyses. All analyses were performed using the Statistical Package for the Social Sciences (12) and data for boys and girls were analyzed separately. In order to determine whether differences in physical growth and development were attributable to early nutritional history, we performed a MANOVA with age (seven levels) and nutritional history (two levels) as independent variables and all the anthropometric measures as dependent variables. This was followed by an ANOVA for each individual anthropometric measure.

Sexual maturation as assessed by the Tanner scale was similarly analyzed using the MANOVA (nutritional history by age) with all the growth measures as the dependent variables. This was followed by ANOVA for individual measures of sexual maturation. The percentage of index and comparison girls who had achieved menarche at the time of this study were compared using χ^2 analysis and the mean age of onset was compared using a Student's *t* test. Finally, in order to examine the possible role of height and weight in sexual maturation, including age at menarche, the data were analyzed by MANOVA with height and weight entered as covariates.

RESULTS

Anthropometric measures. Mean values of physical growth of index (46 girls and 62 boys) and comparison children are presented in Table 1. For almost every measure, index girls and especially those in the older age group had lower values than did their comparisons, whereas values for index boys were similar to or only slightly lower than those of the comparison boys in all age groups. In order to analyze the overall relationships of nutritional history to physical growth, we applied a 2-way MANOVA with nutritional history (two levels) and age (seven levels) as independent variables and all 10 growth measures as dependent variables. In the case of the girls, the MANOVA confirmed highly significant differences between index and comparison children [$F(10,650) = 3.92; p < 0.001$] and significant age effects [$F(60,429) = 2.06; p < 0.001$]. Similar findings were obtained for the boys, although differences between index and comparison groups were less striking. There was no interaction between age

Table 1. Mean values ($\pm$ SD) of anthropometric measures for children with histories of early malnutrition and the comparison groups at 9 to 15 yr of age

Measures	Male		Female	
	Comparison (n = 64)	Index (n = 62)	Comparison (n = 43)	Index (n = 46)
Ht (cm)	150.40 $\pm$ 12.18	148.92 $\pm$ 12.50	149.63 $\pm$ 11.02	145.25 $\pm$ 11.40
Upper segment length (cm)	69.01 $\pm$ 4.67	68.61 $\pm$ 5.20	69.37 $\pm$ 4.59	66.21 $\pm$ 5.30
Lower segment length (cm)	81.32 $\pm$ 7.89	78.80 $\pm$ 8.26	80.38 $\pm$ 6.95	78.78 $\pm$ 6.62
Upper/lower segment ratio	0.86 $\pm$ 0.04	0.88 $\pm$ 0.06	0.86 $\pm$ 0.05	0.84 $\pm$ 0.05
Wt (kg)	39.37 $\pm$ 10.35	37.02 $\pm$ 10.74	41.90 $\pm$ 11.47	35.42 $\pm$ 7.63
Wt/ht	0.26 $\pm$ 0.05	0.25 $\pm$ 0.05	0.28 $\pm$ 0.06	0.24 $\pm$ 0.04
Arm circumference (cm)	21.01 $\pm$ 2.51	20.72 $\pm$ 2.73	21.77 $\pm$ 3.08	20.38 $\pm$ 1.79
Triceps skinfold thickness (mm)	7.00 $\pm$ 2.71	7.70 $\pm$ 3.98	12.39 $\pm$ 4.86	10.43 $\pm$ 2.78
Subscapular skinfold thickness (mm)	5.86 $\pm$ 1.44	6.20 $\pm$ 2.99	9.66 $\pm$ 4.35	7.73 $\pm$ 2.54
Suprailiac skinfold thickness (mm)	6.00 $\pm$ 2.47	6.17 $\pm$ 3.74	9.95 $\pm$ 5.33	7.83 $\pm$ 3.18

Table 2. F values derived from analysis of variance (nutritional history $\times$ age) of anthropometric measures performed separately for boys and girls

Dependent variables	Independent variables					
	Nutritional history		Age		Nutritional history $\times$ age	
	Male (df = 1, 100)	Female (df = 1, 74)	Male (df = 16, 110)	Female (df = 6, 74)	Male (df = 6, 110)	Female (df = 6, 74)
Ht	4.90*	15.30†	41.34†	27.86†	0.62	0.61
Wt	3.10	28.88†	26.37	21.98†	0.44	0.84
Wt/ht	2.12	28.68†	19.40†	15.91†	0.60	1.01
Arm circumference	0.63	11.02‡	14.88†	6.83†	0.61	0.79
Upper segment length	0.52	29.52†	26.31†	23.10†	1.33	0.63
Lower segment length	7.94‡	4.32*	38.34†	19.18†	0.44	0.98
Upper/lower segment ratio	5.74*	5.29*	7.96†	1.54	1.27	1.45
Triceps skinfold thickness	0.20	4.96*	0.90	1.45	0.57	1.11
Subscapular skinfold thickness	0.76	8.24‡	2.22*	4.11‡	0.93	1.62
Suprailiac skinfold thickness	0.10	5.75*	1.67	3.79‡	1.57	0.55

* $p < 0.05$.† $p < 0.001$.‡ $p < 0.01$.

and the nutritional history of the child. In summary both index boys and girls had reduced physical growth relative to comparison children of the same sex and age, although this effect was greater among the girls.

The results of analyses of the individual measures of growth are summarized in Tables 1 and 2 and are described below. It should be noted that height and weight are the most sensitive indicators of previous infantile malnutrition.

Height. Figures 1 A and B show the mean heights at each age plotted against the 10th, 50th, and 90th percentiles of the 1977 National Center for Health Statistics curves for children (13) and Table 1 summarizes these mean values. For both boys and girls, the comparison children fell at or near the 50th percentile. Whereas index boys were reduced at younger ages, they did not differ from comparison boys at 15 yr of age. However, index girls were shorter than comparison girls at all ages. These data were analyzed using univariate analysis of variance (nutritional history by age) separately for boys and girls (Table 2). As may be seen, both index boys and girls were significantly shorter, but this effect was more significant for index girls.

In contrast, when we examined rate of growth by comparing heights at the time of this study with heights achieved 4 yr earlier, we found a higher rate of growth for index girls than for any other group. Index girls grew approximately 25 versus 22 cm for comparison girls, whereas index boys had the same growth

increment as their matched comparisons (about 23 cm). ANOVA showed differences in rate growth to be significantly higher for index girls [$F(1,690) = 5.4$; $p < 0.05$], whereas index and comparison boys did not differ. Age effects were present for both boys and girls, because of rapid growth at this age period, but there was no interaction between nutritional history and age.

Body segment length. These data are summarized in Tables 1 and 2. Although both boys and girls with histories of malnutrition were shorter than their age-matched comparisons, the relative reduction in length of upper (sitting height) and lower body segments (leg length) differed between the sexes. Thus, index girls had a significant reduction in upper body length, and index boys had a significant reduction in lower segment length. Age effects were present for both of these measures of length, but there was no interaction of age and nutritional history for these measures.

Weight. Figures 2 A and B present the weights of children in the study plotted against the standard percentiles of the 1977 National Center for Health Statistics growth curves. As may be seen, comparison girls fell at about the 50th percentile of the US standard, whereas the weights of index girls, which were similar to those of the comparison group at 9 yr of age, declined over time, and by 13 yr of age and beyond, there were very large differences between index and comparison girls. In contrast, index and comparison boys differed only very little at all ages. It

Fig. 1. Height for age in males (A) and females (B).

Fig. 2. Weight for age in males (A) and females (B).

should be noted, however, that comparison boys had weights only at about the 25th percentile of the US standard, and thus, the relative reduction among boys was less. These observations were confirmed by analysis of variance, which showed significant differences in weight between girls with and without histories of malnutrition, but not between boys from the two groups (Table 1). Age effects were also significant, and there was no interaction between nutritional history and sex. These findings persisted even when mean weights were corrected for height (Tables 1 and 2) with values for index girls only being significantly reduced.

Arm circumference. These findings were similar to those reported for weight (Tables 1 and 2). Thus, significant effects of nutritional history were found for girls but not for boys, since

comparison girls had much higher values than any of the three other groups.

Skinfold thickness: (triceps, subscapular, and suprailiac). As may be seen in Table 1, in each instance values for skinfold thickness were higher for girls than for boys. The relative reduction in skinfold thickness was greatest among index girls, in contrast to similar values for index and comparison boys. Analysis of variance confirmed significant reductions for index girls over all ages, but there was no such reduction among the boys (Table 2). Thus, skinfold thickness appears to be an especially sensitive measure of nutritional history for girls. This finding is probably a result of delayed sexual maturation in the index girls which is described in the next section.

Sexual Maturation. Menarche. We found that the onset of menarche was delayed in girls with histories of malnutrition. Thus, at 11 yr of age, 20% of the comparison group had achieved menarche as contrasted with none of the index girls, and at 12 yr these percentages were 75 and 0%, respectively, for comparison and index girls. At 15 yr of age, all comparison girls had achieved menarche, but 40% of the index girls were still premenarchal. In total, 44% of the 43 comparison girls aged 9 to 15 yr had achieved menarche as contrasted with only 22% of the 45 index girls ($\chi^2 = 3.86$; $p < 0.05$). Among the girls who had achieved menarche, the mean age of onset for the comparison group was 11.7 ± 1.1 yr of age, and for the index group, 12.9 ± 0.7 yr. This delay of slightly more than 1 yr was significant by a Student's *t* test [t ($df = 27$) = 3.23; $p < 0.01$].

Tanner scale. Breast and pubic hair development were assessed in girls and genitalia and pubic hair were assessed in boys. A MANOVA with all measures of sexual maturation as the dependent variables confirmed significant effects of prior nutritional history for girls [$F(2,73) = 5.69$; $p < 0.01$], but not for boys of this series since index girls were delayed relative to controls. Age effects were significant for both boys [$F(18,336) = 7.77$; $p < 0.001$] and girls [$F(12,148) = 9.93$; $p < 0.001$]. These analyses were supplemented by univariate ANOVA for each measure which are summarized in Table 3. Briefly, ratings on the Tanner scale for both breast and pubic hair development were significantly lower at all ages in index girls. The data for pubic hair development are presented in Table 4 and are similar to those observed for breast development. As may be seen, index girls are delayed, until 13 yr of age but thereafter they appear to catch up.

The analyses of age of menarche and sexual maturation were repeated controlling for weight and height, since reductions in these may have contributed to the observed findings. ANOVA with height and weight as covariates showed that delays in sexual development of girls in this population were largely accounted for by the reduction in height and weight in the sample since the effects of nutritional history were eliminated in this further analysis. Thus, sexual maturation was delayed in girls with histories of malnutrition, and this finding was associated with reduced height and weight.

DISCUSSION

The current study examined physical growth and sexual maturation in a population of Barbadian children, aged 9 to 15 yr, who were hospitalized with a moderate to severe episode of malnutrition in the 1st yr of life and a matched comparison group. In earlier studies conducted when the children were 5 to

Table 3. *F* values derived from analysis of variance (nutritional history $\times$ age) of Tanner scale ratings of sexual maturation, performed separately for boys and girls*

Dependent variables	Independent variables		Nutritional history $\times$ age
	Nutritional history	Age	
Male	($df = 1, 112$)	($df = 6, 112$)	($df = 6, 112$)
Public hair	3.58	37.65†	1.27
Penile development	1.50	38.20†	0.65
Testicular development	3.15	46.94†	0.76
Female	($df = 1, 74$)	($df = 6, 74$)	($df = 6, 74$)
Breast	4.5‡	31.47†	0.96
Pubic hair	11.25§	26.39†	0.74

* The significant effect of nutritional history in females is not present when this analysis was repeated using height and weight as covariates.

† $p < 0.001$.

‡ $p < 0.05$.

§ $p < 0.01$.

Table 4. Percentage of girls achieving scores of 1 (prepubertal) to 5 (adult development) on the Tanner scale for pubic hair growth

Age (yr)		<i>n</i>	Scores on Tanner scale				
			1	2	3	4	5
9	Comparison	2	50.0	50.0	0	0	0
	Index	3	66.7	33.3	0	0	0
10	Comparison	13	46.2	46.2	0	7.7	7
	Index	8	75.0	25.0	0	0	0
11	Comparison	5	20.0	40.0	20.0	20.0	0
	Index	8	62.5	37.5	0	0	0
12	Comparison	4	25.0	0	25.0	25.0	25.0
	Index	3	0	66.7	33.3	0	0
13	Comparison	9	0	0	44.4	44.4	11.1
	Index	12	8.3	41.7	25.0	16.7	8.3
14	Comparison	7	0	0	0	71.4	28.6
	Index	6	0	0	16.7	66.7	16.7
15	Comparison	3	0	0	0	33.3	66.7
	Index	5	0	0	0	40.0	60.0

11 yr of age, we reported that height and arm circumference were reduced in girls and especially in older girls in this population, but not in boys (3). Weight for height was not reduced in either boys or girls in the previous study. These deficits were not significantly associated with growth patterns of the mothers, who had similar heights and weights regardless of their child's nutritional history or differences in socioeconomic conditions.

We have now extended these observations to 15 yr of age and have found that the growth deficits observed 4 yr earlier are still evident, especially in girls. However, the yearly increment in height (velocity) is the same for both comparison and index groups in the case of boys and significantly higher for index girls than comparison girls. This implies that the *current* status of the index group is not adversely influencing the rate of increase in height. Thus, the velocity of growth during adolescence does not show evidence of retardation due to the early history.

These data conform with those of Dreizen *et al.* (14) in their study of 30 Appalachian girls who were chronically undernourished during childhood. These authors observed delayed physical development including reduced height in the index girls which later caught up due to an increased adolescent growth velocity; however, other studies of the long-term effects of previous infantile malnutrition in Uganda (15) and South Africa (16) show persistent deficits in height among index children up to 18 yr of age, but these studies are limited to single observations of final height. This does not allow determination of differences in velocity between malnourished and well-nourished groups. Thus, the adolescent catch-up by girls with histories of infantile malnutrition remains controversial.

In contrast, mean weights and weights/heights differentiated the index and comparison girls, especially from 13 to 15 yr of age (Fig. 2B). This reduction is also reflected in arm circumference and skinfold thickness in the two groups of girls. These findings can be linked to the delay in sexual development among girls, but not boys with histories of malnutrition. Thus, the mean age of menarche was delayed by 1.2 yr, and there was a corresponding delay in breast and pubic hair development. The relationship between weight gain and menarche has been investigated by Frisch and Revelle (17) who propose the necessity of reaching a critical weight to achieve the onset of menstruation, although this concept has been challenged by Ellison (18). In our population, further analysis which controlled for weight and height eliminated the significant effects of nutritional history on sexual malnutrition. This implies that the delays observed in the index girls are associated with the reduction in weight and height. The delay in onset of adolescence and menarche has been associated with periods of undernutrition during growth (14, 19). However,

these studies do not distinguish between current undernutrition and malnutrition of early childhood. Our study demonstrates that a single early episode of malnutrition during the 1st yr of life is sufficient to cause a delay in menarche onset and the sexual maturation of girls.

The question thus arises concerning the nutritional status of the comparison and index girls. By North American standards, the pubescent comparison girls have a weight which approximates the 50th percentile and the index group lies at the 25th percentile or lower. Since sexual maturation is delayed in the index girls, it is likely that at least part of this failure to gain weight and to accumulate additional body fat as rapidly as the comparison girls is due to delayed endocrine development. Thus, pubescent and postpubescent girls characteristically have increased body fat, as reflected in increased skinfold thickness as compared with less mature girls (20). Furthermore, medical examination and hematologic findings did not distinguish between index and comparison groups. It should be noted that the standards for height, weight, arm circumference, and skinfold thickness for the index group are at least as good as Cuban and Jamaican standards (21) for their normal populations, suggesting that the comparison Barbadian girls may be accumulating excessive amounts of body fat. In fact obesity is a known health problem in adult Barbadian women (Ramsey F, personal communication), as it is in black US populations (20).

The possibility of a greater proportion of genetic late maturers in the index group cannot be entirely eliminated. However, early malnutrition, which is significantly correlated with these delays in physical growth and sexual maturation, seems a more obvious interpretation. Moreover, delays in sexual maturation are also seen following other childhood diseases such as hypothyroidism suggesting that endocrine development is sensitive to a variety of insults, including infantile malnutrition.

Finally, these data cannot be explained on the basis of differential treatment of boys and girls in Barbados. In an earlier paper of this series, we reported on the behavior at home of children in the study and found no differences in the parent-child interaction in relation to sex or nutritional history of the child (6). Socioeconomic status and home environmental conditions were also similar for boys and girls.

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